## Remarks

The specification has been amended to include a claim to priority in compliance with 35 U.S.C.§119(e).

The Claims have been amended in accordance with 37 C.F.R. 1.121 and a clean copy of the claims as amended has been included as a courtesy.

Claims 2-8, 10-13, and 16-28 have been cancelled without prejudice.

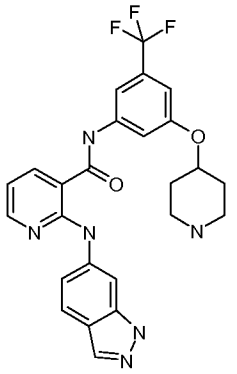
Claim 1 has been amended to narrow the claim to one preferred embodiment wherein $R^1$ is phenyl having a particular substitution pattern together with certain preferred selections for the other substituents. Support for this embodiment is found throughout the specification and particularly at page 14, lines 12-15 of the PCT as published (WO 2004/094380), which is preferred embodiment of paragraph 42). Method of treatment Claim 14 (and so also Claim 15 dependent thereon) has likewise been narrowed to recite compounds of this same preferred embodiment.

New Claims 29 - 32 mirror amended Claims 1, 9, 14 & 15, but are drawn to a second preferred embodiment of the compounds of the present invention wherein $R^1$ is heterocycle having a particular substitution pattern together with certain preferred selections for the other substituents. Support for this second claimed preferred embodiment is found throughout the specification and particularly in the preferred embodiment of paragraph 10) (page 12, lines 31-32), combined as provided at page 14, lines 24-26, with the preferred embodiment of paragraph 40) (page 14, lines 8-9)(all references are to the PCT as published).

Claims 1-4 currently stand rejected under 35 U.S.C. 102(b) in view of Pruecher, Gaster and Eriksson. Each of these references describe similar compounds wherein $R^1$ is methyl. The present amended claims require $R^1$ to be substituted phenyl (Claims 1, 9, 14 &15) or unsubstituted or substituted pyridinyl or thiophenyl (Claims 29-32). Thus the cited references clearly do not anticipate the presently presented Claims and withdrawal of the rejection is respectfully requested.

Claims 1-5 and 9 currently stand rejected under 35 U.S.C. 102(a), (b), or (e) in view of Chen or Askew. Chen discloses kinase inhibitors for the treatment of various cancers. The compounds disclosed in the Chen reference all have a common core of a heterocyclic moiety having an amino-linked heterocycle substituent (either bicyclic or monocyclic with a second cyclic moiety directly bonded to the first) and a second amide linked substituent. In this reference, it is permitted and once exemplified (1 of 475 exemplified compounds) that this amide

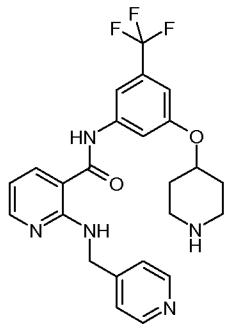
linked moiety be a pyridinyloxyphenyl moiety as cited in the Office Action (RN 454481-41-5 is example 74 in the reference):



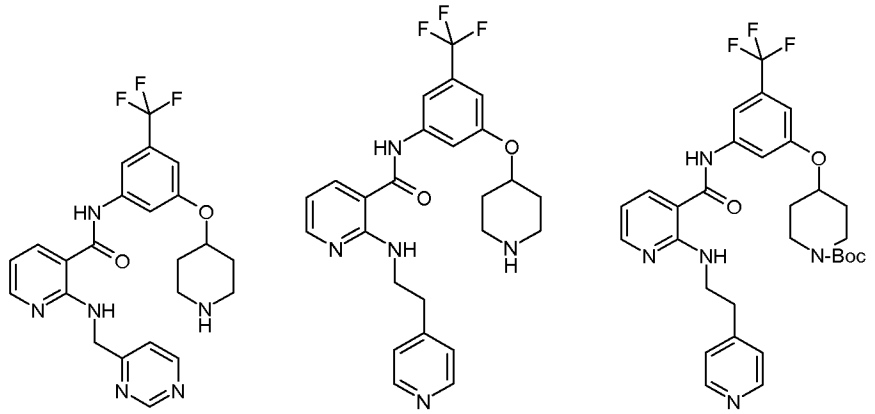
In this reference example, the pyridyl moiety roughly corresponds to $R^1$ of the presently claimed compounds, wherein $R^1$ is substituted heterocycle, which would here be substituted pyridyl. It is noted that the amine-linked heterocyclic moiety in all of the reference compounds, in this example, indazol-6-yl-amino, form an integral part of the compounds disclosed in the reference.

However, it is noted that the presently claimed compounds do not allow such substitutions on the $R^1$ moiety (see page 8, lines 13 through page 9, line 15). Specifically, $R^1$ substituents according to the present description may not be amine linked substituents and may not be bicyclic moieties, let alone bicyclic heteroaryls as described in the Chen reference. Therefore, the Chen reference can not be said to anticipate the compounds of the present invention. Withdrawal of the rejection is respectfully requested.

The Askew reference is related to the Chen reference (assigned to Amgen, shares 11 of 21 inventors, is drawn to compounds of a similar structure for treatment of the same indications and shares the same priority filing dates) and similarly discloses kinase inhibitors for the treatment of various cancers. As in the Chen reference, a large substituent off the core structure of the Askew compounds may be selected to be an amide linked pyridinyloxyphenyl moiety, and such is exemplified in example 533, RN 453561-92-7, as cited in the Office Action:



Three other compounds of the 1194 examples in the Askew reference have amide linked pyridinyloxyphenyl moieties: Examples 543, 838, and 839, respectively:




As with the analysis in regard to the Chen reference, it is noted that the presently claimed compounds do not allow amine linked substituents on $R^1$ as described in the Askew reference, which amine-linked heterocycles form an integral part of all the reference compounds. Therefore, the Askew reference can not be said to anticipate the compounds of the present invention. Withdrawal of the rejection is respectfully requested.

Claims 1-7, 9, and 14-15 currently stand rejected under 35 U.S.C. 112, first paragraph. In the Examiner's estimation, Applicants' showing of compounds having potent agonist activity at the 5-$HT_{1F}$ receptor coupled with evidence correlating such activity with a therapeutic benefit is insufficient to enable the presently claimed invention. Examiner places on Applicants the further arbitrary requirement that evidence be shown that the presently claimed compounds solve an additional technical problem, to wit, the crossing of the blood brain barrier, using statements in the Phebus reference as a basis for making such a requirement. Further the Examiner considers the Specification lacking in sufficient guidelines as to how to use the compounds to operate the method of treating/preventing migraine.

It is first noted that it has never been a requirement under U.S. patent law that clinical data be required to enable a pharmaceutical composition of matter claim or a pharmaceutical method of treatment claim. To comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). It is in fact long been held as sufficient to show an in vitro activity such as receptor binding affinity, combined with some reasonable nexus between that in vitro activity and the therapeutic benefit claimed. The Specification points out this correlation in the background and in the biological sections of the application, particularly by reference to the

detailed correlation between 5-$HT_{1F}$ receptor activity and migraine found in US Patent 5,708,008 (page 163, line 6). The present discovery is of novel, non-obvious 5-$HT_{1F}$ receptor agonists, where it is known that agonism of the 5-$HT_{1F}$ receptor may reasonably be expected to have therapeutic benefit in the treatment or prevention of migraine by virtue of this activity.

Further, it is respectfully submitted that the Examiner has overlooked or ignored the description of formulation and administration of compounds of the present invention for the claimed methods of treatment found in the Specification at page 170, line 15 through page 173, line 19. This description clearly informs one of ordinary skill in the art how to work the methods of treatment/prevention.

Lastly, though it is not necessary for a finding of enablement as discussed above, the Examiner seems to have also overlooked or ignored the protein extravasation assay described in the Specification at page 166, line 11 through page 167, line 25, which assay is an in vivo rat assay, which would not be effective if the test compounds did not effectively reach the target tissues. There is therefore no basis for a rejection based on description or enablement for the Claimed compounds or the Claimed methods of treatment utilizing the compounds. Withdrawal of this rejection is kindly requested.

Claims 14-15 currently stand rejected currently stand rejected under 35 U.S.C. 112, first paragraph. In the Examiner's estimation, a claim for the prevention of migraine requires showings of specific dosages different from those described in the Specification as noted above along with evidence of non-toxicity at such doses, as well as a 100% cure rate. The Examiner is referred to the above arguments as they pertain directly to this second rejection based on section 112. Examiner is also directed to M.P.E.P. 2164.01(c), 2nd paragraph

> "For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. The applicant need not demonstrate that the invention is completely safe. See also MPEP § 2107.01 and § 2107.03."

The asserted additional requirements for clinical data are simply not the law with regard to methods of treatment. Note that there is no claim limitation to the exact dose to be used or that such dose be free of any associated toxicities. (Again, "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). It is in fact well known in the art how to determine if a patient is a candidate for preventative treatment for migraine. The National Migraine Association website states:

> First, preventive, or prophylactic, medications are prescribed to prevent or reduce the number of attacks in patients who experience frequent Migraines, typically two or more per month. In general, these medications act over time to prevent blood-vessel swelling; however, they do not treat the Migraine-associated symptoms and are non-selective. Many sufferers using preventive treatments will still have to take attack-aborting medications to relieve pain and other symptoms.
>
> Women's Health Channel states:
>
> > Prophylactic Treatment: Preventative medication may be prescribed for patients who have frequent headaches (3 or more a month) that do not respond to abortive treatment. Studies have shown that as many as 40% of these patients may benefit from preventative treatment.

It is well within the skill of the art to take the guidance given as referenced above to set appropriate dosing for any given clinical candidate selected among the compounds within the scope of the claims and for a physician to adjust such dosing as needed for a given patient under their care. Furthermore, it has never been a requirement that a pharmaceutical agent provide a 100% cure rate to be patentable. Withdrawal of the rejection is respectfully requested.

Lastly, Claims 1-7, 9, and 14, currently stand rejected (presumed to be provisionally rejected in light of the copending nature of the cited application) on the ground of nonstatutory obviousness-type double patenting over U.S. Application 10/569,109 in view of King. Respectfully, Examiner misapplies the King reference. King teaches that it would be obvious to try certain types of modifications as points of departure in furthering development of a given SAR (structure-activity relationship). Without some teaching in the art that a given substitution is in fact a bioisostere, there is no expectation that the substitution will maintain the desired activity. It is just as well known that making similar substitutions may well be the solution to eliminate an undesired activity or induce/significantly enhance a desired activity. Otherwise there is no point in making the substitution; there is no value in making a compound with the *same* activity as the one known, the point being to modify the activity profile of the compound to discover something better.

In the instant case, the substitution of an amino linkage with an ether/thioether is a significant change. Amino groups and ether/thioether groups have significantly different properties, both in terms of synthetic/metabolic chemistry and in terms of pharmaceutically relevant molecular interaction. Amino groups are basic and often hydrogen bond acceptors, whereas ethers/thioethers tend to be the opposite. Such a radical alteration to the core structure would not lead one of ordinary skill in the art to any reasonable expectation that activity would be maintained. Therefore it can not be said that the '109 Application would render present

application obvious, nor vis versa. As such, the present double patenting rejection is inappropriate and its withdrawal is respectfully requested.

In view of the foregoing amendments and remarks Applicants respectfully submit that all rejections have been obviated or overcome and that Claims 1, 9, 14, 15, and 29-32 set forth an invention that is new, useful, and unobvious, and which is therefore deserving of patent protection. Passage to Issue of the present application is believed to be in order, and is respectfully requested.

Please charge any fees or credit any overpayment in connection with this application that may be required by this or any related paper to Deposit Account No. 05-0840.

If the Examiner has any questions, or would like to discuss any matters in connection with this application, the Examiner is invited to contact the undersigned at (317) 433-9829.

Respectfully submitted,

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